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Figure 1

5'~~~~~3' Immunostimulatory oligonucleotide

Immunomers

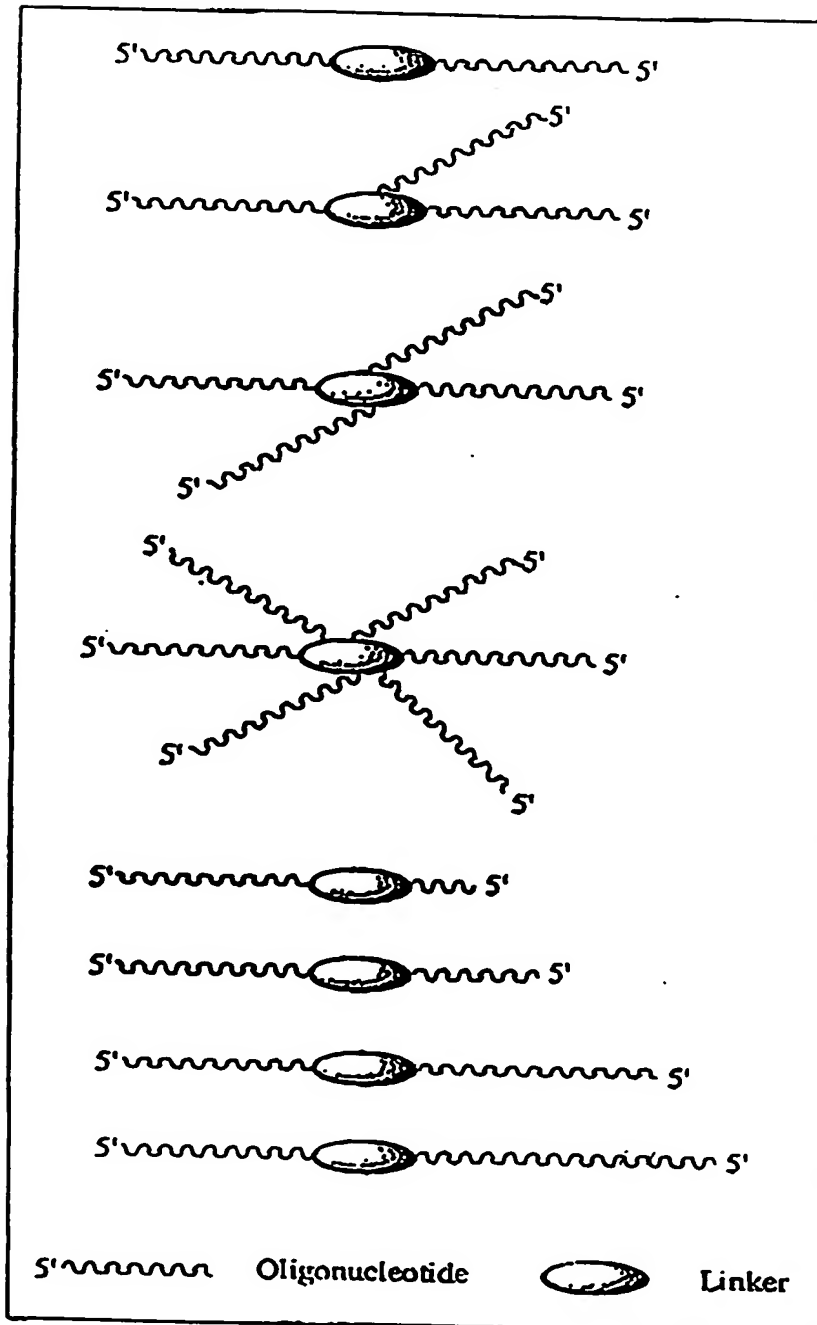


Figure 2

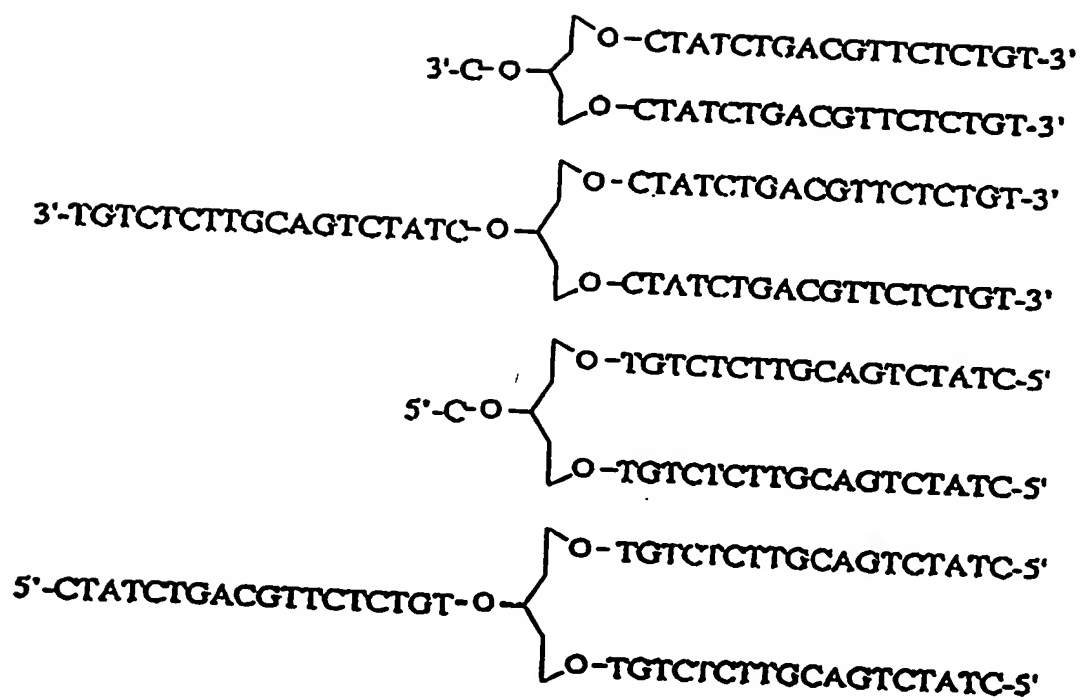


Figure 3

Linkers for linear synthesis

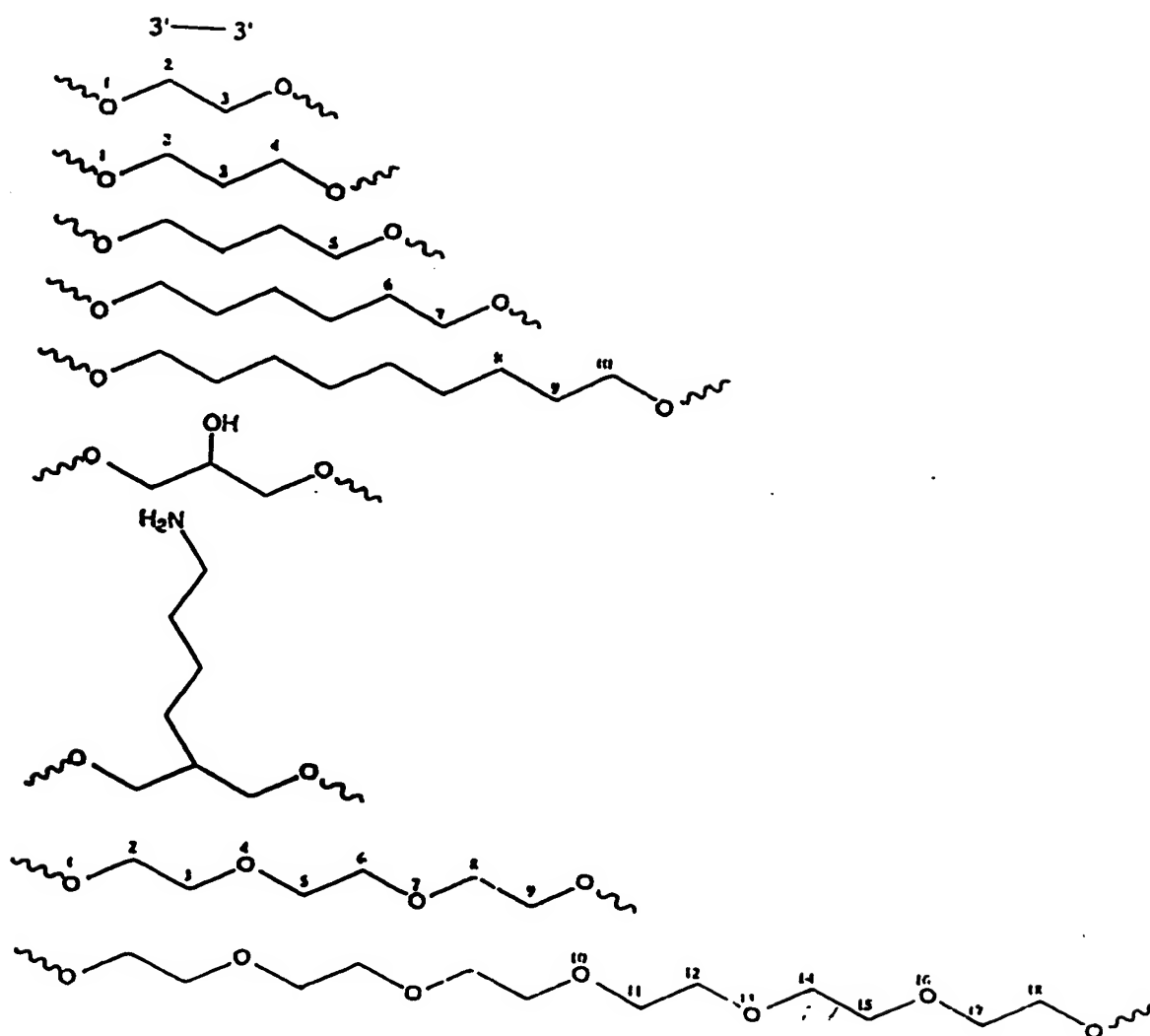
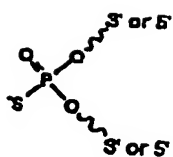
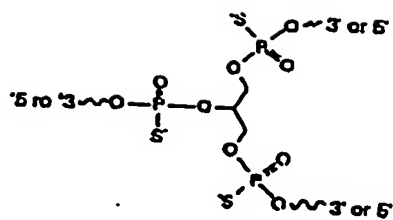


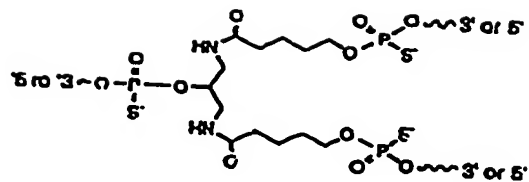
Figure 4



No linker



S, Glycerol brancher,  
Short linker



II, Sym. brancher,  
Long linker

Figure 5

# Linear Synthesis of Immunomers

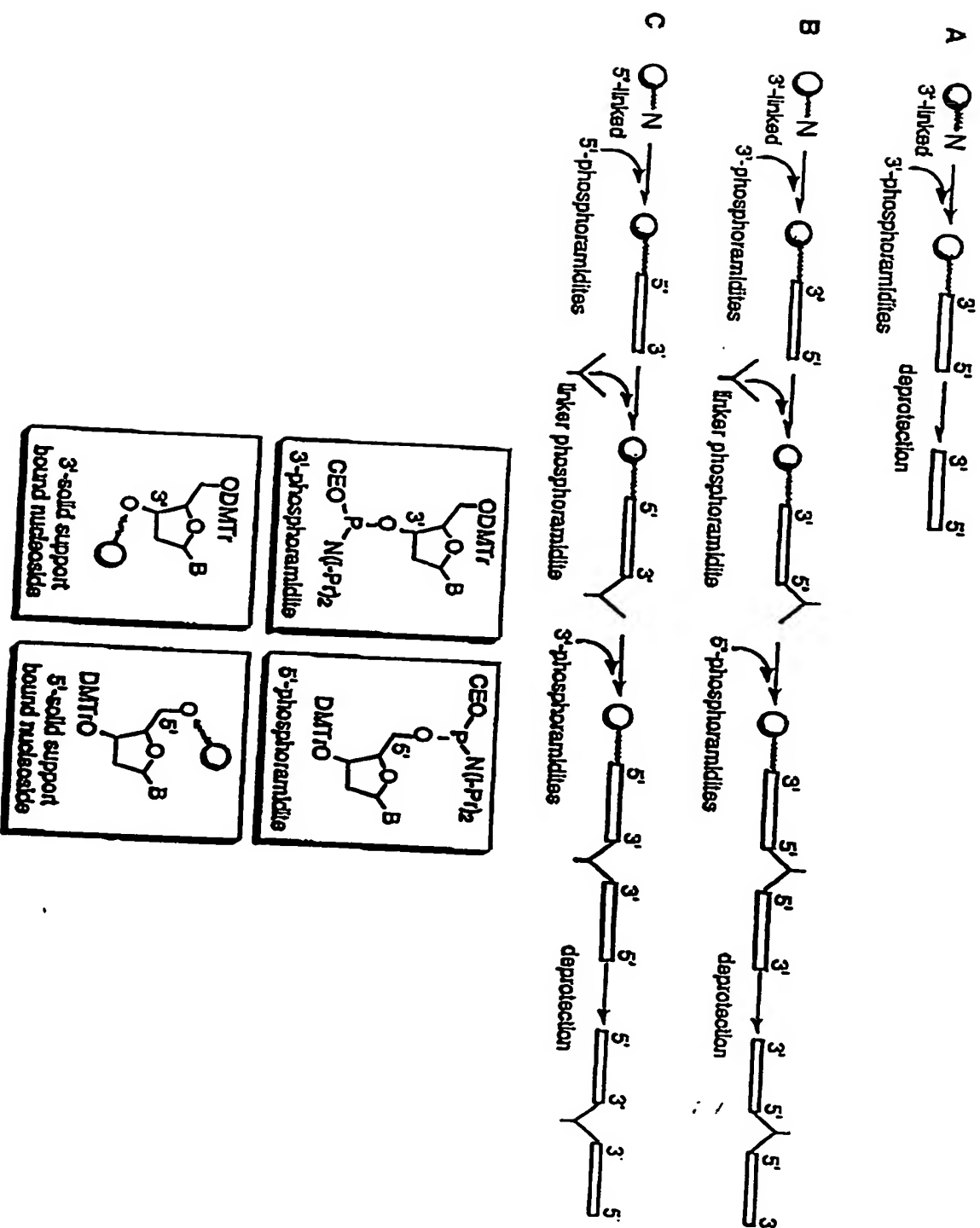


Figure 6

# Parallel Synthesis of Immunoiners

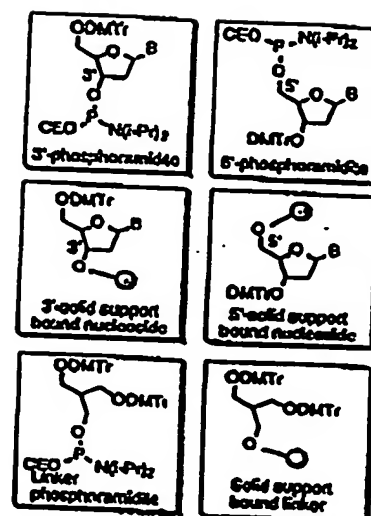
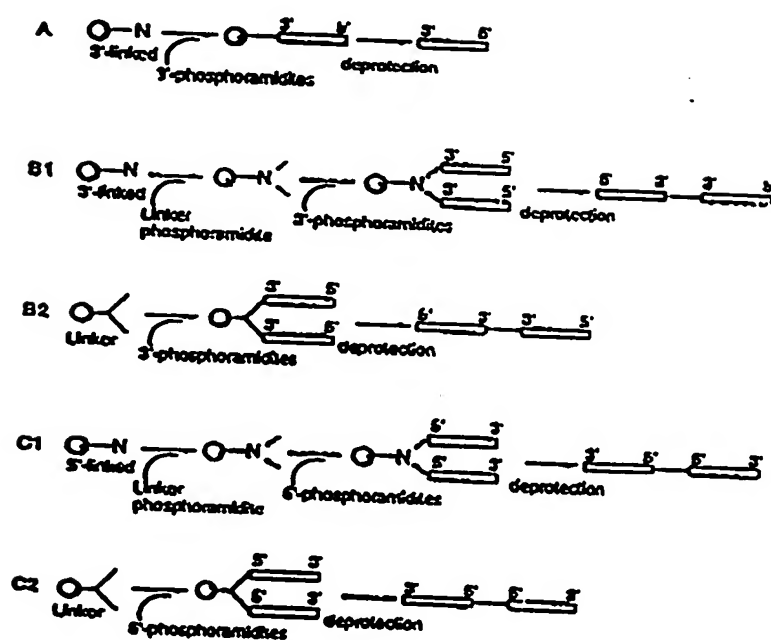


Figure 7A

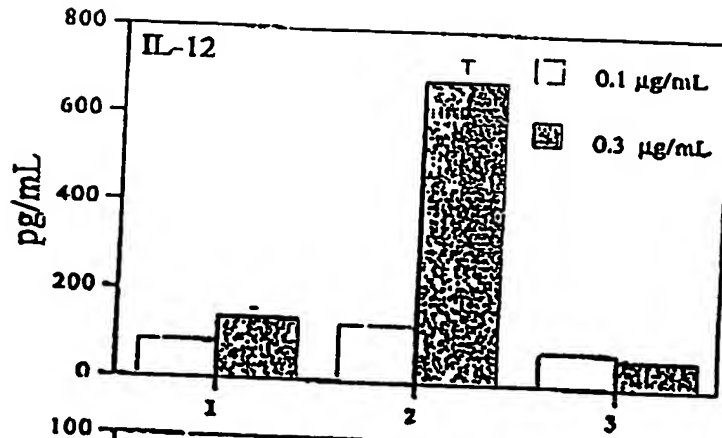


Figure 7B

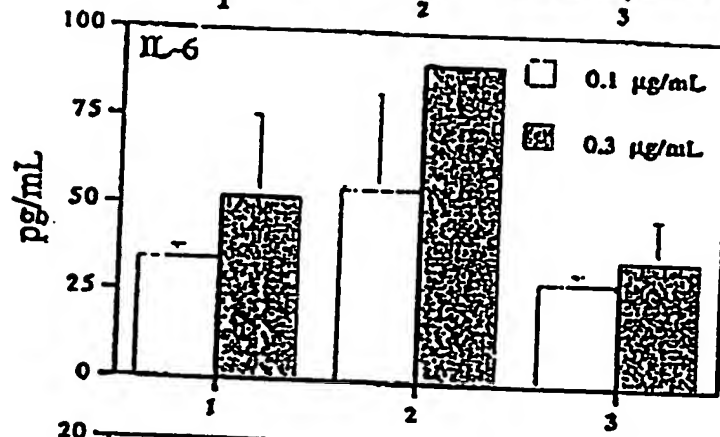


Figure 7C

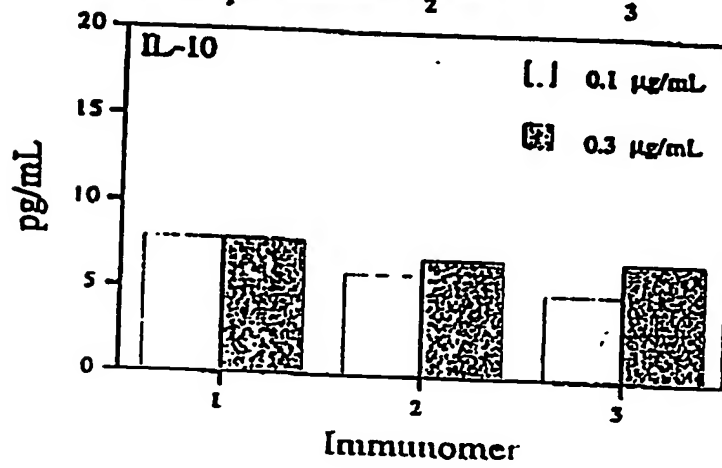




Figure 8A

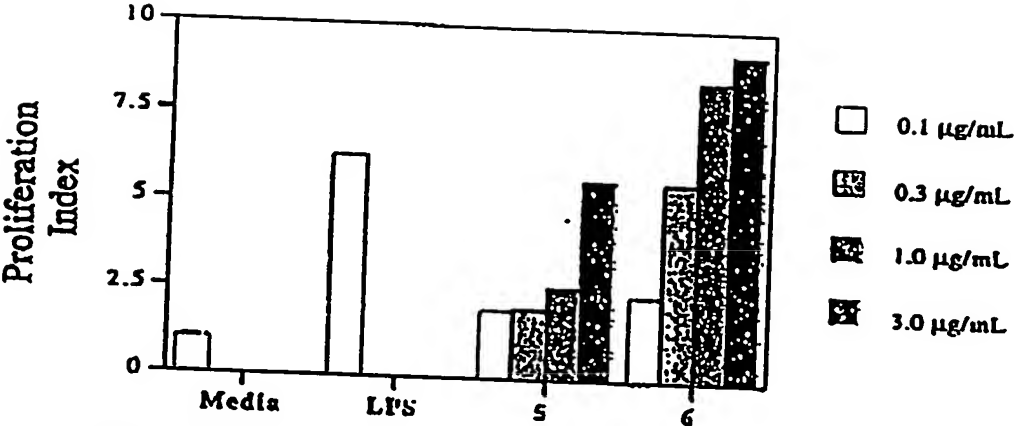


Figure 8B

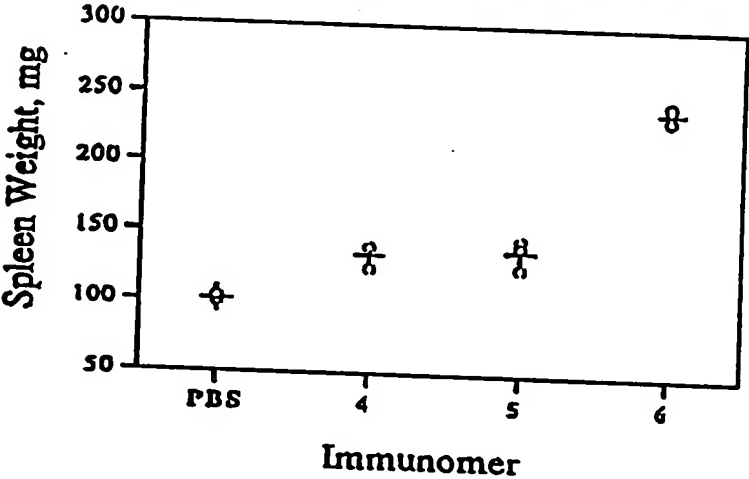


Figure 9A

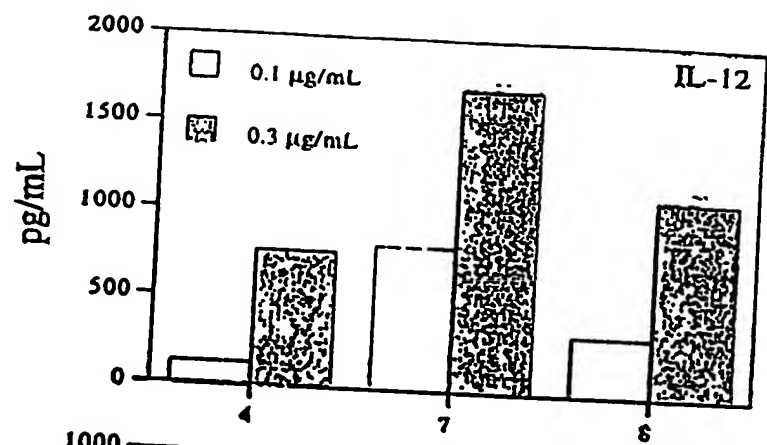


Figure 9B

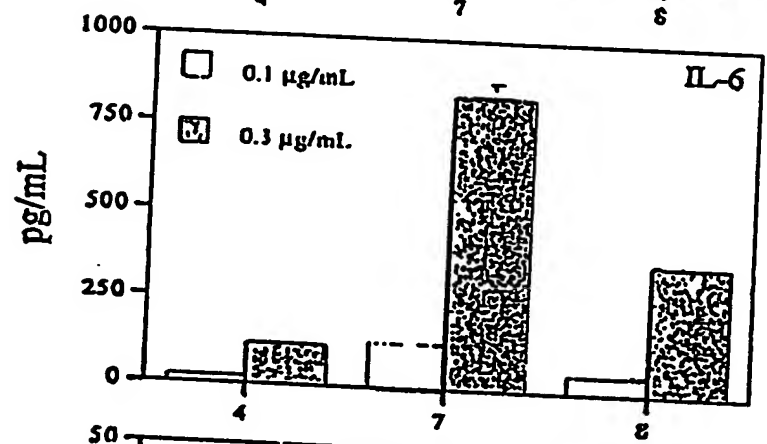


Figure 9C

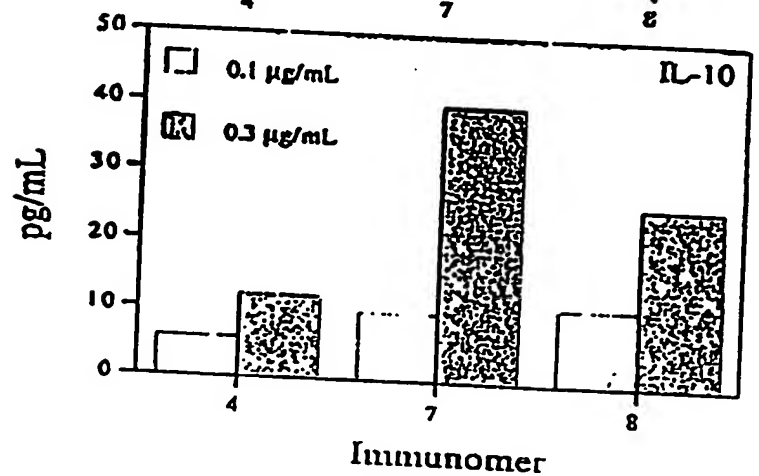


Figure 10A

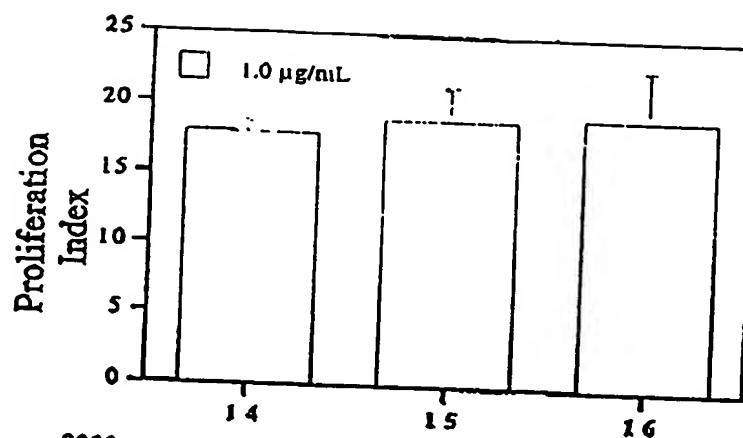


Figure 10B

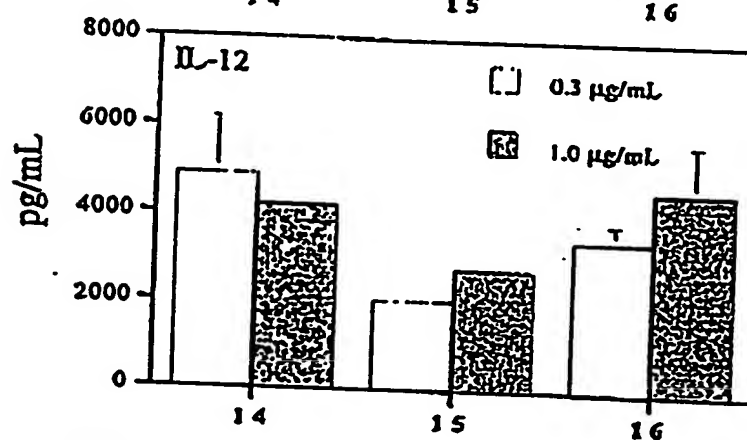


Figure 10C

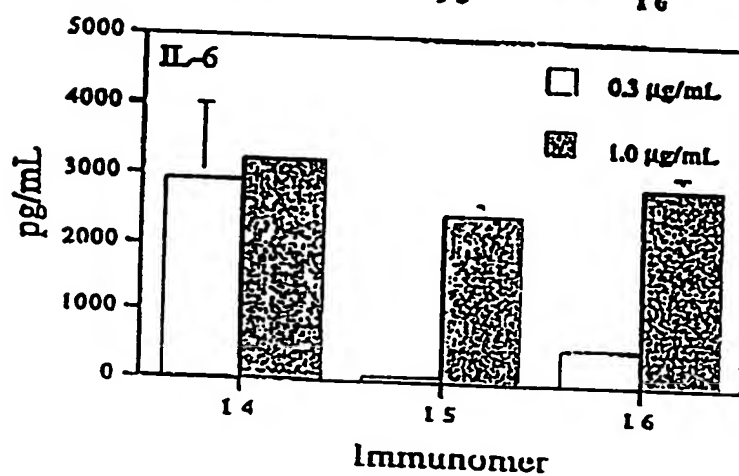


Figure 11A

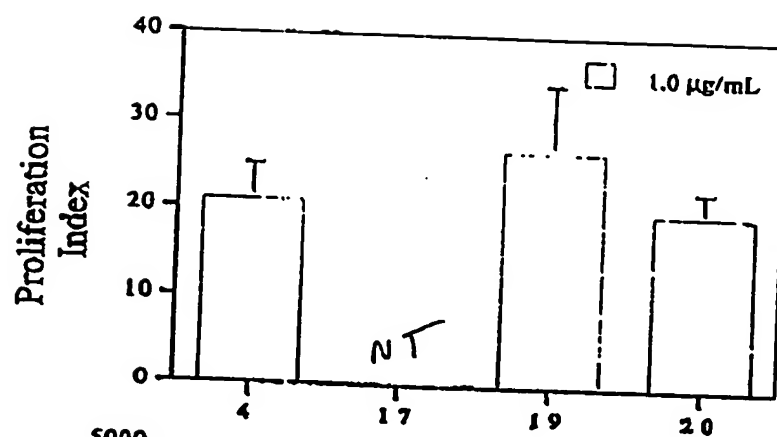


Figure 11B

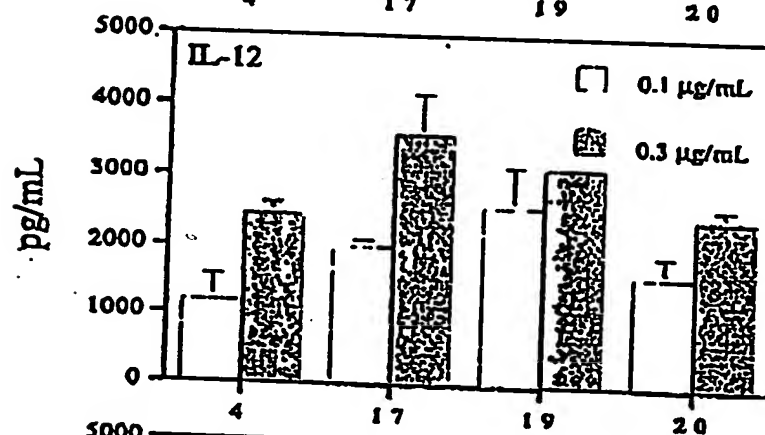


Figure 11C

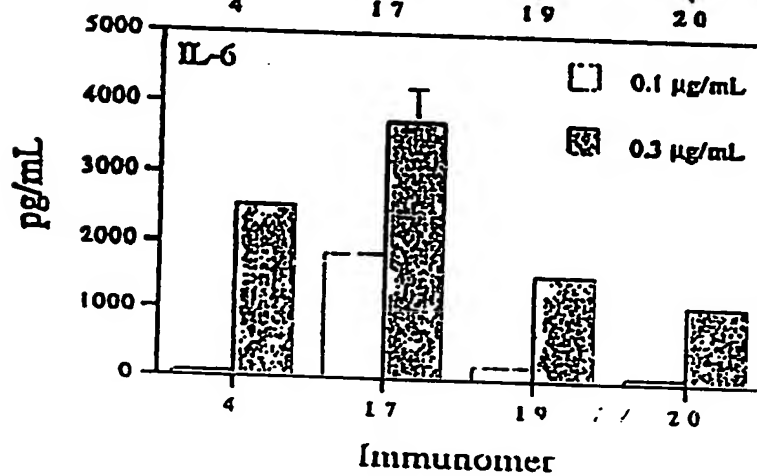


Figure 12

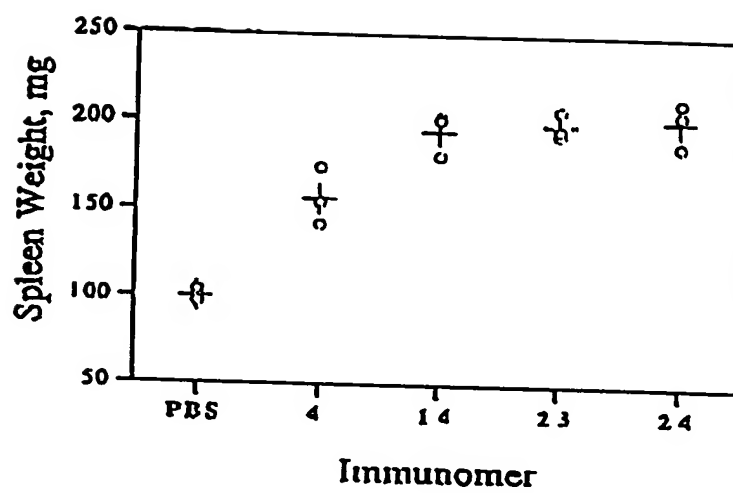
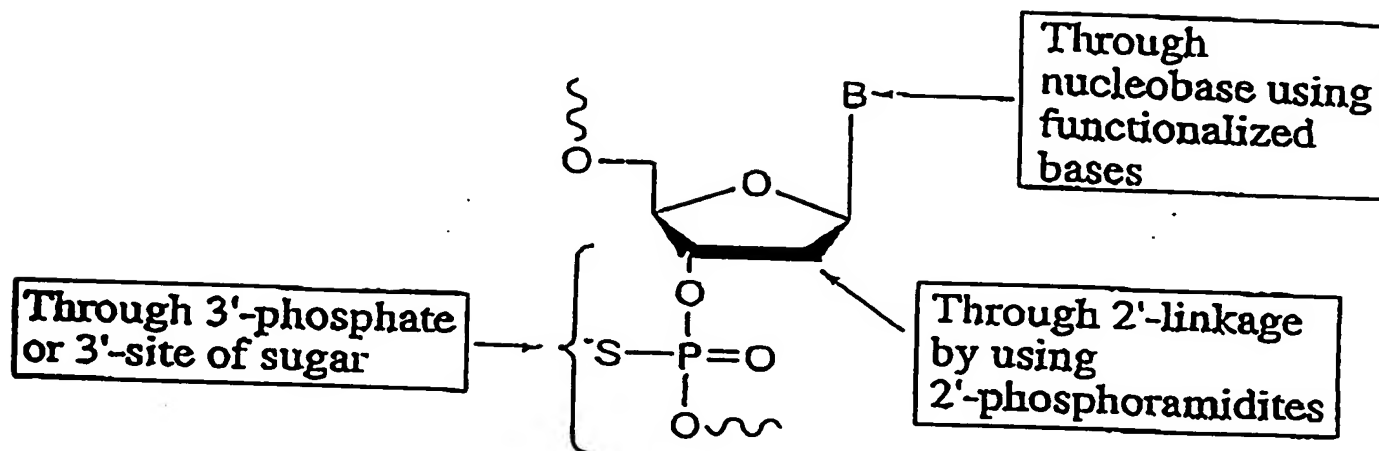
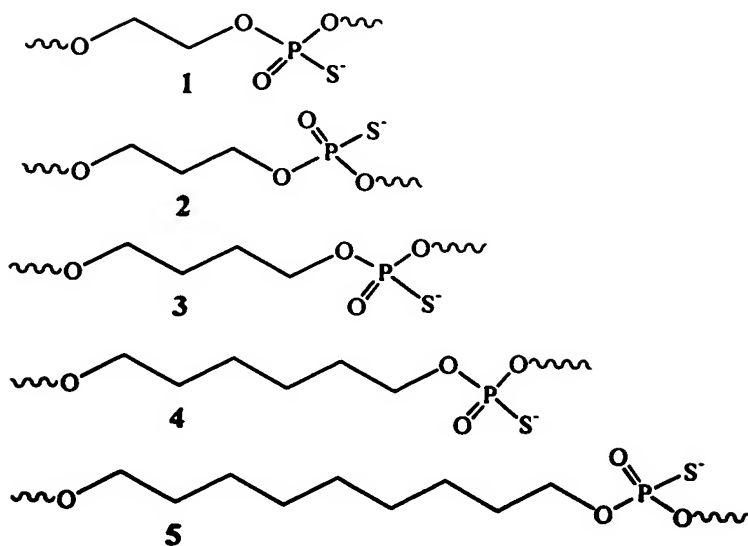


Figure 13

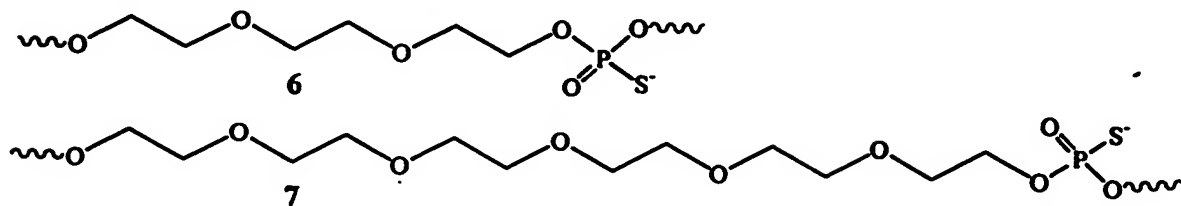
Possible sites for conjugation



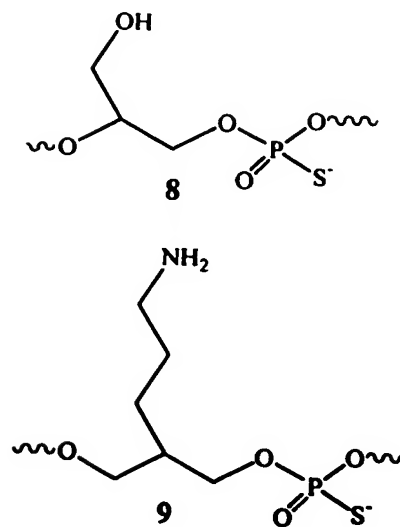
**A. Alkyl linkers**



**B. Ethylene-glycol linkers**



**C. Branched alkyl linkers**



**Figure 14**

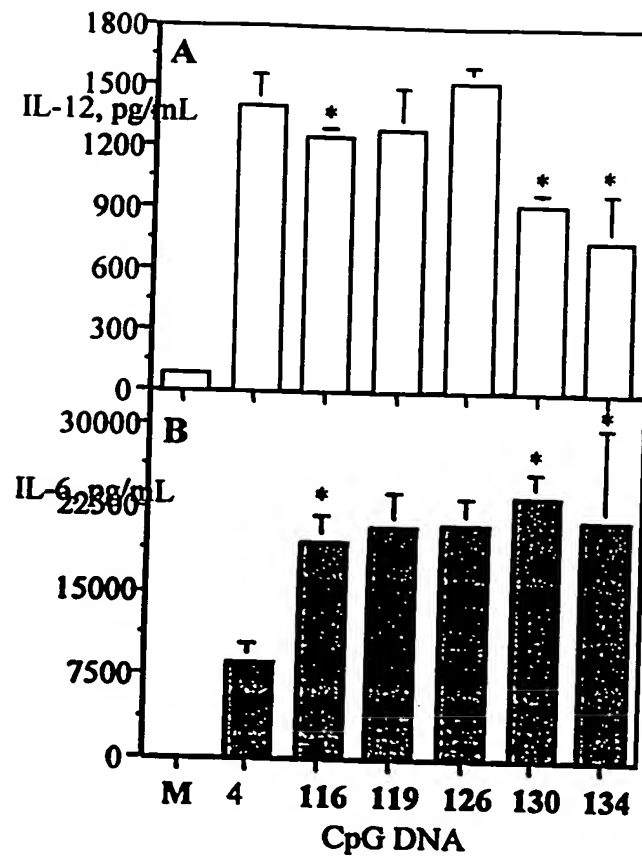


Figure 15



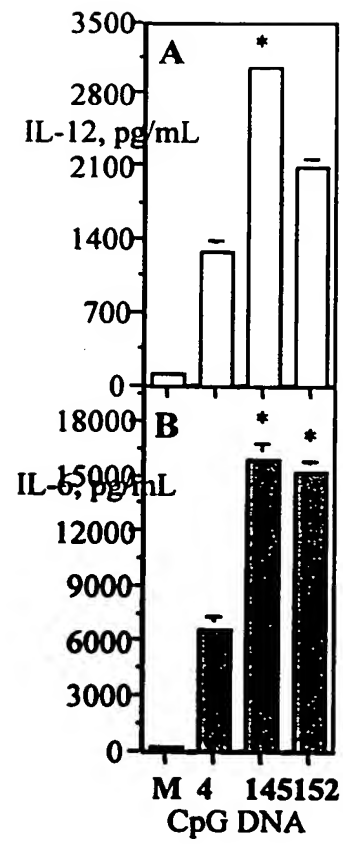


Figure 16

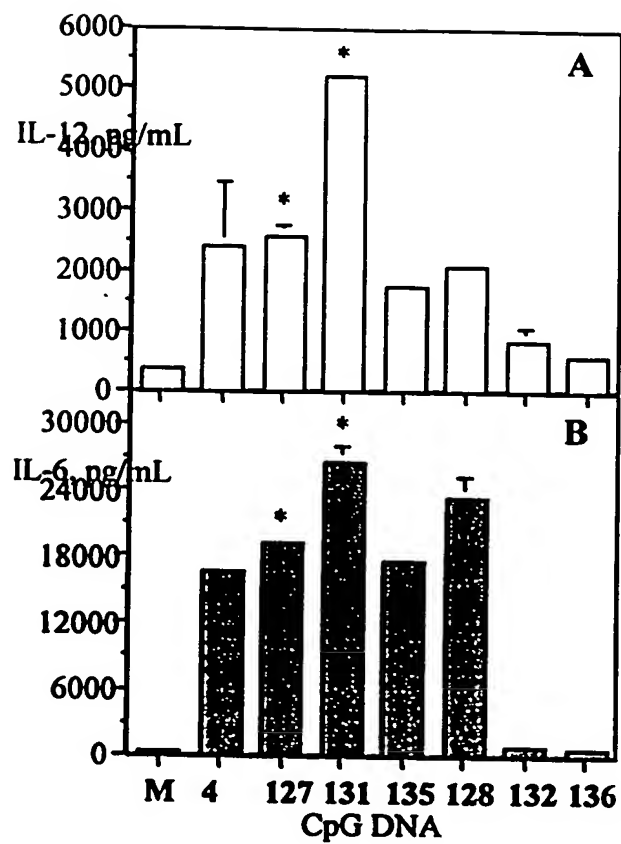


Figure 17

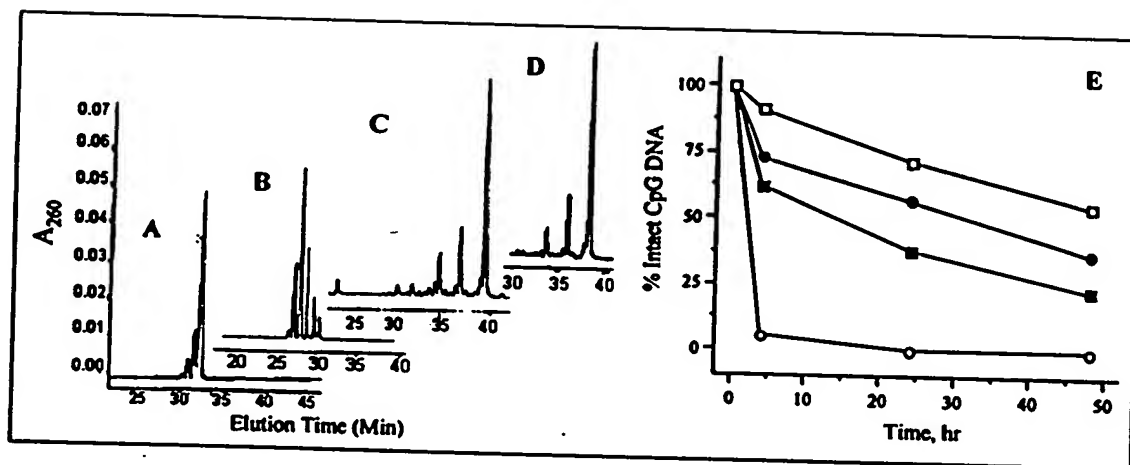


Figure 18

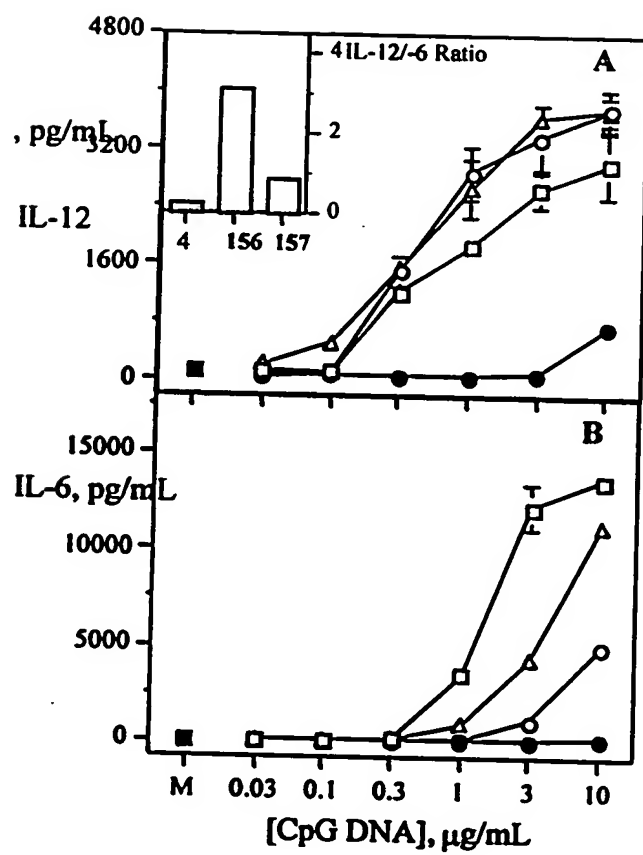


Figure 19

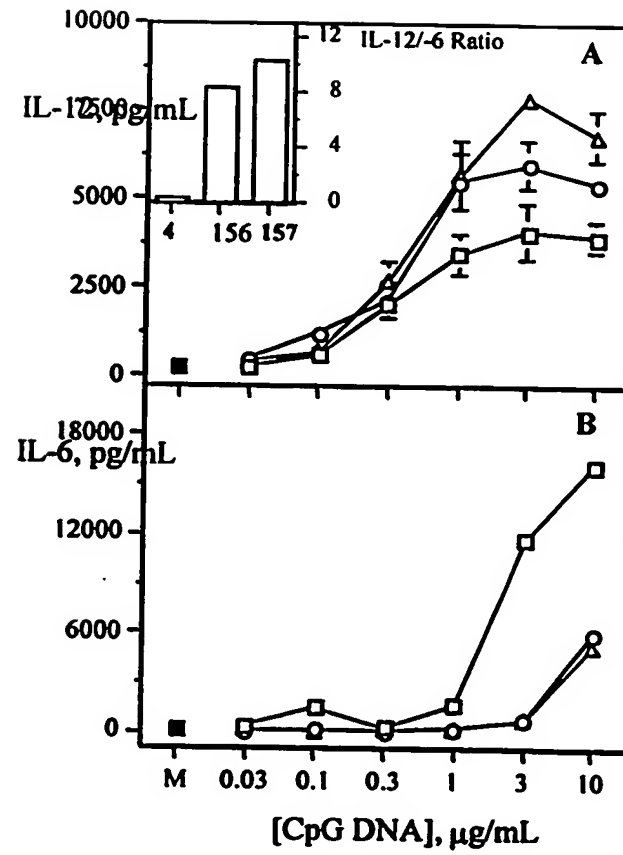


Figure 20

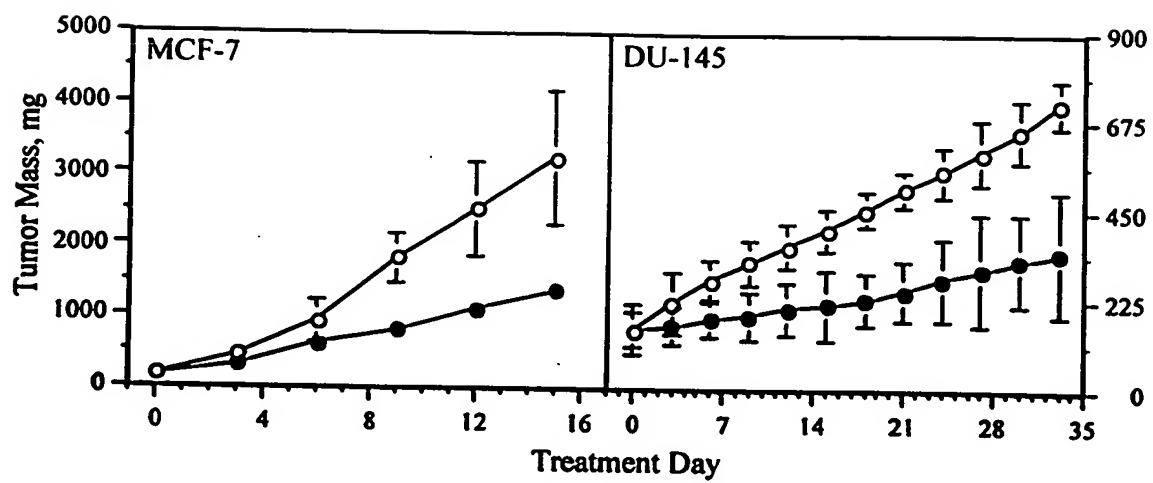
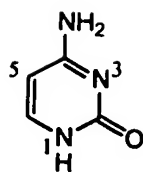
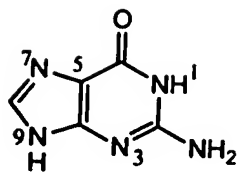


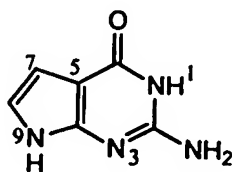
Figure 21



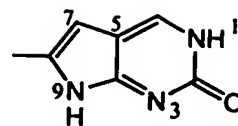
2-Oxo-4-amino pyrimidine or cytosine



2-Amino-6-oxo-purine  
or guanine



2-Amino-6-oxo-7-deazapurine  
or 7-deaza-guanine



2-Oxo-7-deaza-8-methyl-  
purine

FIGURE 22

- 1 d(5'-CTATCTGACGTTCTCTGT-3')
- 2 d(5'-CTATCTGARGTTCTCTGT-3')
- 3 d(5'-CTATCTGACRTTCTCTGT-3')
- 4 d(5'-CTATCTGTCGTTCTCTGT-3')
- 5 d(5'-CTATCTGTRGTTCTCTGT-3')
- 6 d(5'-TCTGARGTTCT-L-TCTTGRAGTCT-5')
- 7 d(5'-TCTGTRGTTCT-L-TCTTGRTGTCT-5')

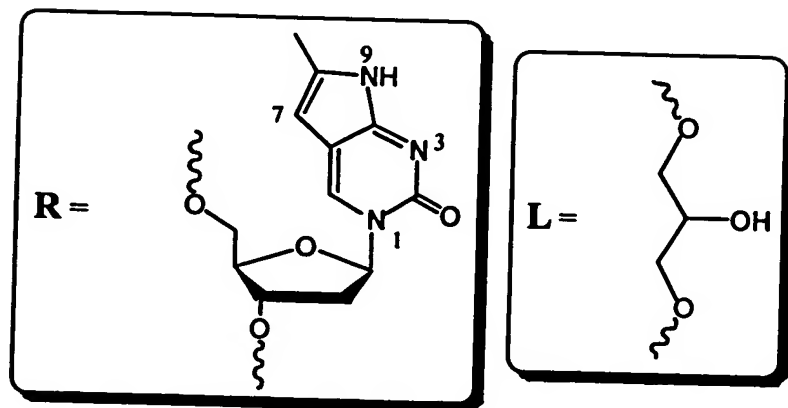


FIGURE 23



Comparison of Natural Pyrimidine-Purine Immunostimulatory Motif  
and Synthetic-Purine-Guanine Immunostimulatory Motif (RpG)

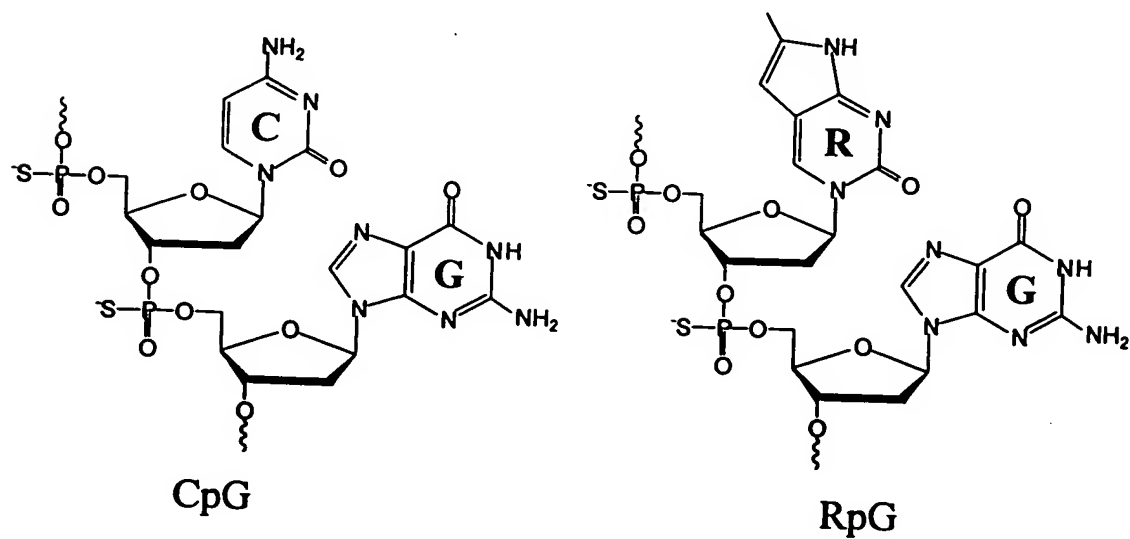


FIGURE 24

Immunostimulatory activity of parent oligonucleotide 1 containing CpG dinucleotide motif, oligonucleotide 2 containing RpG dinucleotide motif and control oligonucleotide 3 containing GpR dinucleotide motif in mouse spleen cell culture assays. All sequences contain mouse-specific immunostimulatory motif (GACGTT).

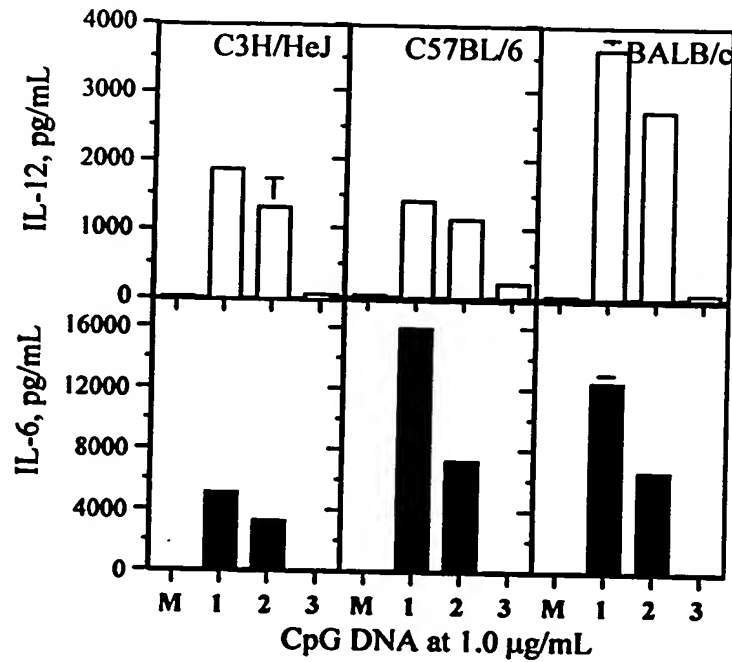


FIGURE 25

Immunostimulatory activity of parent oligonucleotide 4 containing CpG dinucleotide motif, and oligonucleotide 5 containing RpG dinucleotide motif in mouse spleen cell culture assays. All sequences contain human-specific immunostimulatory motif (GTCGTT).

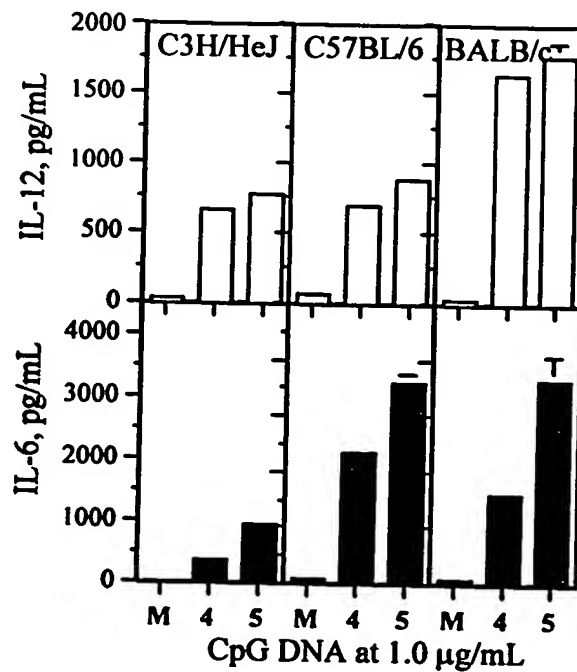


FIGURE 26

Immunostimulatory activity of parent oligonucleotides 1 and 4 containing CpG dinucleotide motif, and immunomers 6 and 7 containing RpG dinucleotide motif in mouse spleen cell culture assays. Sequences 1 and 6 contain mouse-specific immunostimulatory motif (GACGTT) and sequences 4 and 7 contain human-specific immunostimulatory motif (GTCGTT).

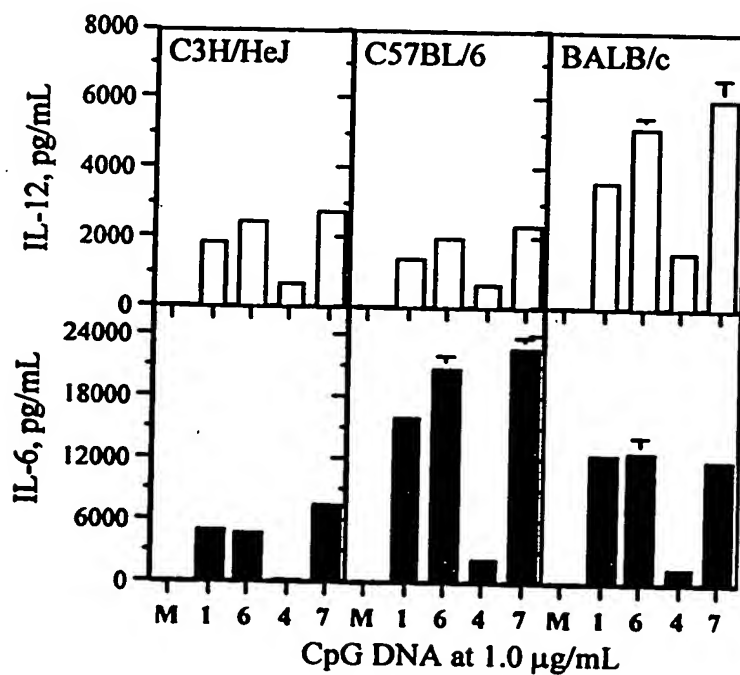


FIGURE 27

Immunostimulatory activity of parent oligonucleotides **1** and **4** containing CpG dinucleotide motif, and immunomers **6** and **7** containing RpG dinucleotide motif in J774, macrophage-like cell culture assays. Sequences **1** and **6** contain mouse-specific immunostimulatory motif (GACGTT) and sequences **4** and **7** contain human-specific immunostimulatory motif (GTCGTT).

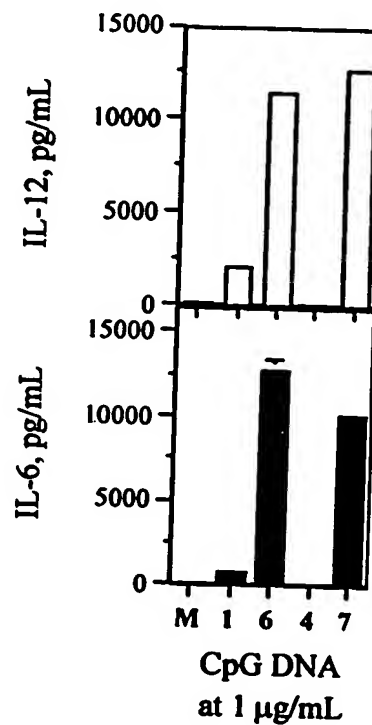


FIGURE 28

Activation of NF- $\kappa$ B and degradation of I $\kappa$ B $\alpha$  in J774 cells as a measure of immunostimulatory activity of parent oligonucleotides 1 - 7.

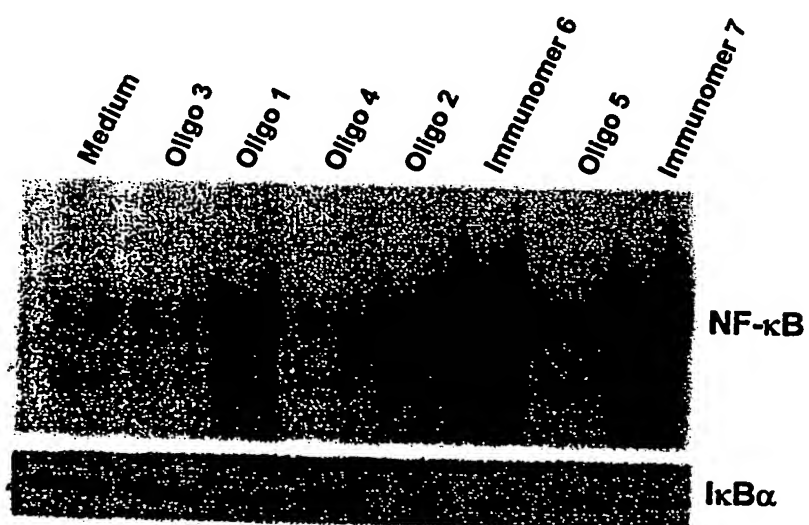


FIGURE 29

Immunostimulatory activity of immunomer 7 human PBMC cultures (one donor) at 10  $\mu\text{g/mL}$  concentration.

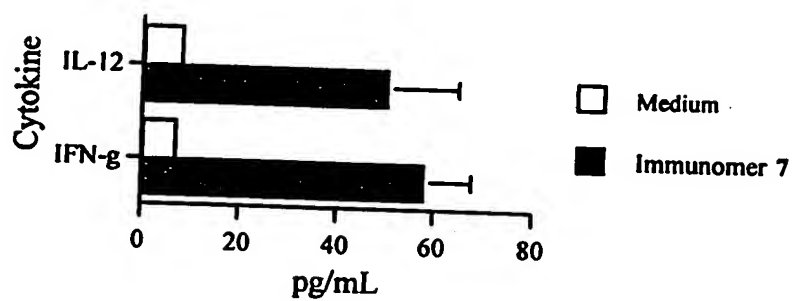


FIGURE 30